Docket No. PRD2166USPCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Marc Karel Jozef Francois	Confirmation No: 1592
Serial No.	:	10/585,754	Art Unit: 1624
Filed	:	July 12, 2006	Examiner: Adam C. Milligan
For	:	MITRATAPIDE ORAL SOLUTION	

The Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND APPEAL BRIEF UNDER 37 CFR § 41.37

Dear Sir:

This Second Appeal Brief is in response to the non-Final Office Action mailed October 29, 2010 (NFOA), which reopened prosecution in response to the first Appeal Brief filed on July 30, 2010. A Notice of Appeal was originally due on January 29, 2011. This Appeal Brief is timely since it is being filed no later than February 28, 2011 together with a Second Notice of Appeal and a one month extension of time.

I. Real Party in Interest

The real party in interest is Janssen Pharmaceutica N.V. to which the inventors have assigned their rights and which is a subsidiary of Johnson & Johnson.

II. Related Appeals and Interferences

None.

III. Status of Claims

Rejected: Claims 1 and 3-12

Allowed: None

Withdrawn: Claim 13

Objected to: None

Cancelled: Claim 2

Appealed: Claims 1 and 3-12

IV. Status of Amendments

No amendments were filed after the non-Final Office Action of October 29, 2010.

V. Summary of Claimed Subject Matter

The following summary is for the purpose of complying with the provisions of 37 C.F.R. § 41.37(c)(1)(v). The entire disclosure should be reviewed to obtain a complete understanding of the claim language.

Claim 1

Claim feature	Citations to specification
An oral solution comprising mitratapide or a pharmaceutically acceptable salt thereof,	Paragraphs [0002], [0010], [0011]
a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C,	Paragraphs [0010], [0012]-[0015]
a taste modifying agent	Paragraph [0010], [0017], [0018]
and an antioxidant,	Paragraphs [0010], [0020]-[0022]
wherein the pharmaceutically acceptable solvent is selected from the group consisting of dimethyl isosorbide, diethylene glycol monoethyl ether, caprylocaproyl macrogol-8 glyceride, propylene glycol monolaurate, polyethyleneglycol 200, polyethyleneglycol 300 and polyethyleneglycol 400, and mixtures thereof, or mixtures of polyethylene	Paragraphs [0012]-[0014]

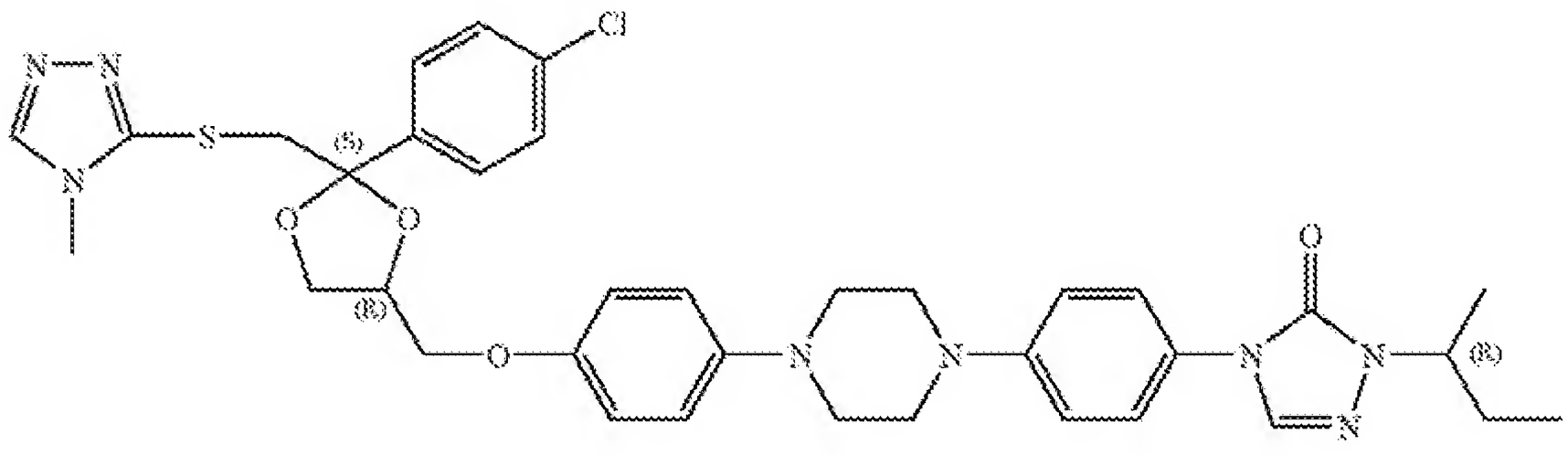
glycols (PEGs) having an average molecular weight higher than 400 with PEGs having an average molecular weight lower than 400	
so that the mixture thereof is liquid at room temperature.	Paragraph [0012]

VI. Grounds of Rejection to be Reviewed

- Claims 1 and 3-12 under 35 U.S.C. §103(a) as being unpatentable over Heeres (WO96/13499) in view of Basit (The Effect of Polyethylene Glycol 400 on Gastrointestinal Transit: Implications for the Formation of Poorly Water Soluble Drugs, Pharmaceutical Research, Volume 18, No. 8, 2001) and Chen (US2002/0147201).

VII. Argument

It is believed that a brief review of technology involved in this appeal would be helpful to the merits panel reviewing this appeal. The claims are directed to an oral solution of mitratapatide or a pharmaceutically acceptable addition salt thereof. "Mitratapatide is the International Non Proprietary (INN) name for the compound (-)-[2S-[2.alpha.,4.alpha.(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)- -2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methy]-1,3-dioxolan-4-yl]methoxy-]pheny]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-tria- zol-3-one having the following structure.



."

Specification, [0002]. Mitratapide is known and has been indicated to be useful as a lipid lowering compound, *id.*, [0003]-[0004], and has been formulated as an aqueous solution in the past using a cyclodextrin solubilizing agent. *Id.*, [0007]. However, it was necessary to use high amounts of the solubilizing agent, adjust the pH to 4.0 and use an antimicrobial preservative. *Id.*, [0008]. The resulting aqueous solutions required a high amount of solubilizing agent and did not meet the requirements of the European Pharmacopoeia for the antimicrobial efficacy test. *Id.*, [0009].

In contrast to those mitratapide aqueous solutions, the pending claims feature oral solutions of mitratapide using the specified organic solvents "wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22° C, a taste modifying agent and an antioxidant, fulfill these requirements." Specification, [0010].

A. Separate Argument for Claim 1

i. Legal standards

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the examiner to establish a factual basis to support the legal conclusion of obviousness. *See In re Fine*, 837 F.2d 1071, 1073 (Fed. Cir. 1988). In so doing, the examiner is expected to make the factual determinations set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966). These showings by the examiner are an essential part of complying with the burden of presenting a prima facie case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). If that burden is met, the burden then shifts to the applicant to overcome the prima facie case with argument and/or evidence. Obviousness is then determined on the basis of the evidence as a whole. *Id.*; *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986); *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984); and *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976). Further, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

ii. Claim construction

"[A]s an initial matter, the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

Here, claim 1 is directed to an oral solution of mitratapide or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C. Claim 1 sets forth that the pharmaceutically acceptable solvent is selected from the group consisting of dimethyl isosorbide, diethylene glycol monoethyl ether, caprylocaproyl macrogol-8 glyceride, propylene glycol monolaurate, polyethyleneglycol 200, polyethyleneglycol 300 and polyethyleneglycol 400, and mixtures thereof, or mixtures of polyethylene glycols (PEGs) having an average molecular weight higher than 400 with PEGs having an average molecular weight lower than 400. The specification contains evidence that not every pharmaceutically acceptable solvent will meet the solubility requirement of claim 1. *Id.*, [0013].

iii. Analysis

a. **Heeres**

The Examiner cannot identify a specific embodiment set forth in Heeres that describes an oral solution of mitratapide, let alone an oral solution that possesses the properties featured in claim 1. Rather, the Examiner has cobbled together two different types of disclosure in Heeres in order to form a phantom embodiment that is not explicitly described in the reference. Specifically, the Examiner, without any justification, combined portions of the reference that describe various forms into which the described compounds may be formulated without reference to a specific active ingredient and portions that identify mitratapide as one such compound. The manner in which the Examiner combined these disclosures is strong evidence that the rejection is based upon the hindsight provided by Appellants' own disclosure.

Specifically, Heeres describes a vast genus of compounds. *Id.*, page 1, line 31-page 5, line 4. Mitratapide is described as one of the species included within that vast genus. *Id., e.g.,* page 18, compound 40.[1] Heeres also describes a laundry list of dosage forms in which the disclosed compounds can be used, including oral, rectal and parenteral injection forms. *Id.*, page 10, line 7-page11 line 2. In describing oral dosage forms, Heeres broadly discloses that "any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions" as well as various solid oral dosage forms such as tablets and capsules. *Id.*. Heeres does not specifically link this laundry list of dosage forms to mitratapide.

In order to arrive at an oral composition of mitratapide that is within the scope of claim 1, the Examiner relies upon a portion of Heeres that describes embodiments suitable for parenteral compositions, not oral compositions. NFOA at 3, citing Heeres, p. 10, ll. 16-18 ("[f]or parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included."). Not only is this passage not directed to oral solutions, but it only generically describes parenteral dosage forms for injection with a generic active ingredient. Further, Heeres itself recognizes that oral solutions differ from injectable solutions. Compare "Example 8: Oral solutions" with "Example 11, Injectable solution" where the adjuvants of Example 11 are not coextensive with those of Example 8. Thus, it is error on the Examiner's part to mix and match these disparate disclosures of Heeres in an attempt to arrive at the subject matter of claim 1. Again, this is strong evidence of the use of impermissible hindsight.

b. Chen

Chen describes water soluble and palatable complexes of poorly water soluble pharmaceutically active ingredients in which the active ingredient is

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[1] The Examiner continues to mistakenly identify compound 22 of Heeres as mitratapide. NFOA at 3. Although compound 22 has the same R^1, R^2, R^3 and –X- substituents as mitratapide, it does not have the same stereochemistry or properties as mitratapide, *i.e.*, compound 40.

complexed with glycyrrhizin[2]. *Id.*, [0019], [0035]. "Active ingredient" is broadly defined and exemplified by a long list of pharmaceutical classes of compounds as well as individual drugs. *Id.*, [0020],[[0025] [0027] and [0035].

Chen also describes the use of polyethylene glycol as an optional plasticizer and that antioxidants can be used in the formulations of that reference. *Id.*, [0064], [0076].

c. Basit

Basit describes the results of studies performed to assess the effect of PEG 400 on the solubility of poorly-water soluble drugs. *Id.,* Title, Abstract. Basit states that PEG 400 is widely used as a solubility-enhancing vehicle for drugs. *Id.*, page 1146, right hand column. This is consistent with Appellants' description of PEG 400 in the specification that PEG 400 is the most widely used pharmaceutically acceptable solvent. *Id.*, [0015].

Basit states that "[a]lthough PEG 400 has been widely used in these respects, in some cases the results have been less successful." *Id.* Page 1146, right hand column. In discussing the results from the referenced studies, Basit, indicates that PEG 400 "by means of reducing residence time in the small intestine, is…likely to have a detrimental effect on the rate and/or extent of absorption of drugs." *Id.*, page 1149, right hand column. Basit then concludes that, while PEG 400 will improve the solubility of drugs, the "concurrent reduction in gastrointestinal transit time…may limit the opportunity for drug absorption and nullify any possible bioavailability enhancement. *Id.*.

d. Heeres, Chen and Basit

Combination of these references is improper for at least four reasons. First, the Examiner has impermissibly used the hindsight provided by Applicants' own disclosure. The Examiner, for example, has not presented a fact-based analysis as to why a person of ordinary skill in the art viewing Heeres without knowledge of the present application would select mitratapide from the thousands of active agents disclosed in the reference. *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992). Nor has

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[2] Glycyrrhizin is a naturally occurring flavoring agent found in licorice. *Id.*, [0047]

the Examiner explained why, once having fortuitously chosen mitratapide as the active agent, it would have been obvious to formulate that specific active agent as an oral solution. On this record, the only reasonable conclusion is that the Examiner used the present disclosure and claims as a road map to make these selections since there is no disclosure in Heeres that points to that path. This is the height of impermissible hindsight.

Second, in applying the teachings of Basit to Heeres, the Examiner has misunderstood statements in Basit that clearly teach away from using PEG 400 with the pharmaceutical agents described in Heeres. As explained above, Basit teaches that any benefit in terms of increased bioavailability of an active agent through use of PEG 400 can be nullified by the concurrent decrease in gastrointestinal transit time. In other words, while the use of PEG 400 may increase the bioavailability of an active agent, the use of PEG 400 may also lessen the time the active agent is present in the gastrointestinal. These properties establish that the use of PEG 400 as a pharmaceutical adjuvant is not a predictable field.

Somehow, the Examiner is of the opinion that the statements in Basit regarding the use of PEG 400 reduces gastrointestinal transit time is an advantage that suggests the use of PEG 400 in compositions of Heres. NFOA at 3-4. It is respectfully suggested that the Examiner has misunderstood the import of the teachings of Basit. Again, Basit states that PEG 400 "by means of reducing residence time in the small intestine, is therefore ***likely to have a detrimental effect on the rate and/or extent of absorption of drugs***." *Id.*, page 1149, right hand column. This is a clear teaching that the use of PEG 400 as a drug solubilizer may have a detrimental effect, i.e., the decrease in gastrointestinal transit time is an undesired property. Thus, the use of PEG 400 for this purpose is unpredictable.

"[A reference] must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed.Cir.1987). Here, the Examiner has misunderstood passages of Basit that directly lead away from the claimed

compositions. This is error on the part of the Examiner. When Basit is considered in its entirety it is seen that the present invention involves an unpredictable art area and it is improper for the Examiner to reach the sweeping conclusions that have resulted in the present rejection.

Third, the Examiner has ignored relevant claim language. The oral solution of claim 1 features an oral solution of mitratapide that has a solubility of 5 mg/ml or higher at a temperature of 22°C. The Examiner does not address this claim feature in the latest iteration of the rejection. This is error on the part of the Examiner since obviousness is based upon the subject matter of a claim as a whole. 35 U.S.C. § 103(a). Reference is made to Table1 of the present specification that presents data showing that not all pharmaceutical solvents are useful to achieve such a composition. The data point once again to the unpredictability of this art and the hindsight nature of the present invention.

Finally, the Examiner relies upon Chen only for its disclosure of antioxidants and taste modifying agents. Thus, Chen does not rectify the deficiencies of Heeres and Basit identified above

In view of these errors, it is respectfully requested that the rejection of claim 1 be reversed.

B. Claims 3-12

For the purpose of this appeal, claim 3-12 stand or fall based upon claim 1

Conclusion

For the reasons set forth above, it is believed that the rejection is in error. Appellants respectfully ask the Board to reverse the Examiner's rejection under 35 U.S.C. § 103(a).

Respectfully submitted,

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CLAIMS APPENDIX

1. (Previously Presented) An oral solution comprising mitratapide or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C, a taste modifying agent and an antioxidant, wherein the pharmaceutically acceptable solvent is selected from the group consisting of dimethyl isosorbide, diethylene glycol monoethyl ether, caprylocaproyl macrogol-8 glyceride, propylene glycol monolaurate, polyethyleneglycol 200, polyethyleneglycol 300 and polyethyleneglycol 400, and mixtures thereof, or mixtures of polyethylene glycols (PEGs) having an average molecular weight higher than 400 with PEGs having an average molecular weight lower than 400 so that the mixture thereof is liquid at room temperature.

2. (Cancelled)

3. (Previously Presented) An oral solution as claimed in claim 1 wherein the pharmaceutically acceptable solvent is polyethyleneglycol 400.

4. (Previously Presented) An oral solution as claimed in any of claims 1 or 3 wherein the taste modifying agent is an intense sweetener, a bulk sweetener, a flavouring agent, or a taste masking agent.

5. (Previously Presented) An oral solution as claimed in claim 4 wherein the taste modifying agent is an intense sweetener selected from the group consisting of saccharin, aspartame, acesulfame, cyclamate, alitame, a dihydrochalcone sweetener, monellin, neohesperidin, neotame, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), and the pharmaceutically acceptable salts thereof.

6. (Original) An oral solution as claimed in claim 5 wherein the intense sweetener is present in an amount ranging from 0.1 to 10 mg/ml.

7. (Previously Presented) An oral solution as claimed in claim 6 wherein the intense sweetener is sucralose.

8. (Original) An oral solution as claimed in any of claims 1 to 7[3] wherein the antioxidant is selected from the group consisting of BHA, BHT, propyl gallate, DL-ά-tocopherol, and citric acid, and mixtures thereof.

9. (Original) An oral solution as claimed in claim 8 wherein the antioxidant is present in an amount ranging from 0.1 to 10 mg/ml.

10. (Original) An oral solution as claimed in claim 9 wherein the antioxidant is BHA.

11. (Original) An oral solution as claimed in claim 10 comprising 5 mg/ml mitratapide, sucralose in an amount ranging from 0.5 to 5 mg/ml, and BHA in an amount ranging from 1 mg/ml to 5 mg/ml, dissolved in PEG 400.

12. (Original) An oral solution as claimed in claim 11 comprising 5 mg/ml mitratapide, sucralose in an amount of 2 mg/ml, and BHA in an amount of 2 mg/ml, dissolved in PEG 400.

13. (Withdrawn) A process of preparing an oral solution as claimed in any of claims 1 to 12, characterized in that said process comprises the steps of dissolving mitratapide, the taste modifying agent and the antioxidant in the pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C, and stirring until a homogeneous solution is obtained.

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[3] It is noted that claim 8 improperly refers to canceled claim 2 and multiple dependent claim 4. These errors will be rectified at an appropriate time after the conclusion of this appeal.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.